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Early Post Traumatic Seizures in Military Personnel Result in Long Term Disability

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14. ABSTRACT

This study is predicated on substantial evidence that early post-traumatic seizures occur frequently and create a metabolic crisis that will lead to cell death of hippocampal tissue among persons who have sustained a traumatic brain injury (TBI). Our central hypothesis is that early post-traumatic seizures are acutely injurious due to increases in intracranial pressure and acute edema of the hippocampus leading to delayed long term hippocampal atrophy. This represents a unique translational hypothesis that we are uniquely qualified to study. In this study we plan to perform continuous EEG monitoring of military and civilian TBI patients for the initial 7 days after TBI to assess for non-convulsive seizures. This is followed by evaluating these same subjects at 6 months after injury by volumetric MRI of the hippocampus and cognitive testing to assess for disturbances of memory-related cognition and post-traumatic stress. We have begun to study civilian TBI patients in year 1 and have worked on establishing methodology and connectivity and IRB permission at military sites in year 1.

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ABSTRACT:

This study is predicated on substantial evidence that early post-traumatic seizures occur frequently and create a metabolic crisis that will lead to cell death of hippocampal tissue among persons who have sustained a traumatic brain injury (TBI). Our central hypothesis is that early post-traumatic seizures are acutely injurious due to increases in intracranial pressure and acute edema of the hippocampus leading to delayed long term hippocampal atrophy. This represents a unique translational hypothesis that we are uniquely qualified to study. In this study we plan to perform continuous EEG monitoring of military and civilian TBI patients for the initial 7 days after TBI to assess for non-convulsive seizures. This is followed by evaluating these same subjects at 6 months after injury by volumetric MRI of the hippocampus and cognitive testing to assess for disturbances of memory-related cognition and post-traumatic stress. We have begun to study civilian TBI patients in year 1 and have worked on establishing methodology and connectivity and IRB permission at military sites in year 1.

Subject Terms: Traumatic brain injury, blast injury, seizures, brain atrophy

INTRODUCTION:

Over 20% of brain injured patients have seizures within 1 week after injury when monitored intensively by continuous electroencephalography (cEEG). With the use of continuous EEG monitoring, we have demonstrated that the incidence of electrographic seizures and clinical seizures is higher, in the range of 20-25%. In the study by Vespa et al, seizures occurred within the initial week after injury and were not associated with the specific type of injury (i.e. contusional versus non-contusional). The seizures occurred repeatedly in nearly ¼ of patients are 1/3 of those with seizures had status epilepticus. In over ½ of the patients, the seizures were nonconvulsive in nature and could not be detected without EEG monitoring. Post-traumatic seizures have been associated with neurochemical signs of cellular distress, secondary excitotoxicity, secondary cellular membrane damage and prolonged elevations of intracranial pressure. Seizures can be readily identified and treated during the critical phases of injury, if the appropriate personnel and monitoring are available. In this study we plan to perform continuous EEG monitoring of military and civilian TBI patients for the initial 7 days after TBI to assess for non-convulsive seizures. This is followed by evaluating these same subjects at 6 months after injury by volumetric MRI of the hippocampus and cognitive testing to assess for disturbances of memory-related cognition and post-traumatic stress.

SUMMARY OF METHODS: The design of this study is to perform continuous EEG monitoring of Military TBI patients at acute care hospital for military TBI for the initial 7 days after TBI to assess for seizures and to evaluate these same subjects at 6 months after injury by volumetric MRI and cognitive testing to assess for hippocampal atrophy and disturbances of memory-related cognition and post-traumatic stress.

Experimental Design

Specific Aim 1: To determine the regional seizure focus and secondary epileptic spread regions using continuous electroencephalography in moderate to severe TBI patients.

Rationale: The incidence rate of post-traumatic seizures exceeds 20%, and thus is a major potential secondary injury modality. The region(s) involved in traumatic injury typically demonstrate intraparenchymal bleeding and acute edema and cell loss. Bleeding leads to release of iron into the tissue which is epileptogenic. In addition, the anterior frontal and anterior poles of the temporal lobes are most commonly involved with hemorrhagic injury. These structures have intimate innervation relationship with the hippocampus and surrounding regions. Demonstration of the whether the injury site is the early epileptogenic site and whether the hippocampus is secondarily induced to have seizures.

Hypothesis 1: Seizures will originate from regions that contain a hemorrhagic traumatic lesion(s).

Hypothesis 2: Seizures will secondarily involve mesial temporal structures including the hippocampus as detected by scalp electrodes.

Subjects: 100 TBI patients with GCS 3-13 at a single center over 5 years of study. Age will range from 14-60 years.

Methods: All TBI patients are admitted through the local emergency room and will have a computerized tomographic scan and neurological examination performed. A Glasgow Coma Scale score will be made. All TBI patients will undergo continuous EEG monitoring on TBI patients GCS < 13 and presence of positive findings on CT scan for a minimum of 3 days. All TBI patients with GCS 8 or less will undergo ICP and jugular venous oxygen monitoring as well. EEG will be started in the emergency room or intensive care unit within 12 hours of injury. EEG monitoring will consist of a 21 channel montage using a digital EEG system and permanent storage of EEG for post-hoc analysis. Electrodes will include bilateral true temporal electrodes, and muscle artifact electrodes. The incidence of seizures and the location of inter-ictal electrographic activity will be determined. EEG will be displayed in the ICU and monitored by specially trained nurses to detect electrographic seizures. Automated seizure detection will be employed (manufacturer's proprietary seizure detection algorithm) and manual screening of large segments of the EEG will be done (high speed play of 20 minutes of EEG every 2 hours). Monitoring will be done for the initial 3 days if no seizures occur or as long as needed if a seizure or status epilepticus occurs within the initial 3 days. Electrographic epileptiform activity will be categorized as follows: Type of epileptiform activity, ictal or inter-ictal, the location of activity, the duration of activity, the periodicity, the location of the spread of the activity, the occurrence of a post-ictal suppression of EEG. The spike burden will be

calculated for each patient. The spike burden will consist of the total duration in minutes of inter-ictal or ictal spike discharges in which the spikes occur with a frequency of > 2/10 seconds. An automated spike detection algorithm has been developed to provide this numerical feature (Persist®, Tuscon, Arizona). Other electrographic activity will be characterized for the daily predominant background rhythm, regional slowing in the theta or delta range, the presence of breach pattern, sleep architecture, burst suppression will be determined every 12 hours. In addition, quantitative EEG parameters of total power, percent alpha, and the power ratio index will be automatically calculated each hour. We will examine the raw EEG during the hour in which an increases of 50% above the baseline value of any of these quantitative measures.

A standardized protocol to treat status epilepticus as well as dosage adjustment of anticonvulsants and duration of anticonvulsants based on the presence of seizures and/or inter-ictal epileptiform activity will be carried out at all centers. A detailed list of medication administration will be kept in order to evaluate the influence of sedatives and other medications upon EEG patterns. In addition, a detailed analysis of past medical history and history of ethanol and recreational drugs will be completed for each subject. A standardized approach to sedation and management of elevated intracranial pressure will be followed. A detailed plan for discontinuation of anticonvulsants will be followed for all subjects (see detailed methods).

A standardized MRI protocol will be applied to all subjects. The imaging protocol includes sequences designed to best define traumatic injury in cortical and subcortical regions and includes GRE, FLAIR, High resolution T1 MP-RAGE sequences. MRI compatible fiducial markers will identify the exact location of EEG electrodes. MRI imaging will be done within 24 hours of the injury.

Analysis: For each patient, the focus of the seizures or inter-ictal epileptiform activity as will be enumerated by using the electrode derivation that is generating the highest amplitude (referential to Cz) and phase reversal (double banana bipolar derivations). The duration and repetition rate of the ictal/inter-ictal epileptiform activity will be defined to determine common anatomic locations of involvement and the periodicity of the activity. We will broadly categorize the spread patterns to ipsilateral hemispheric, contralateral generalized, or no spread beyond one electrode derivation. The ictal focus will be identified in each subject and prospectively compared with the corresponding MRI region. The corresponding MRI region will be categorized as being normal (normal ADC, FLAIR, GRE), edematous (FLAIR or ADC change) or hemorrhagic (GRE positive). The percentage of ictal zones exhibiting each MRI type will be enumerated.

Potential Problems and alternative methods: The precision of EEG localization of an epileptic focus is limited by a small number of electrodes. A more numerous array using 32 or 64 channels would improve the specificity but is not practical

given the intensive care unit conditions. Surface EEG will not permit identification of some seizure activity and the investigators are cognizant of the ability of electrocorticography to enhance the detection rate of seizures. We considered sphenoidal electrodes to better characterize mesial temporal lobe onset, but experience at our center demonstrates that true temporal electrodes were as good as the more invasive sphenoidal electrodes (Mintzer, 2002). Electrocorticography is not applicable to the majority of patients because most of not operated, but rather only have intracranial ICP monitors, which typically are remote from the seizure focus.

Specific Aim 2: To determine if early post-traumatic seizures results in acute intracellular edema in hippocampal tissue ipsilateral to the seizure focus.

Rationale: Acute signs of intracellular edema in epileptic brain tissue have been documented after status epilepticus using diffusion weighted MRI (Huffnagel, 2003; Szabo 2005; Bauer, 2006) and increased glucose utilization (Bergnseider, 1997 and preliminary data noted above), but is not clear whether an acute seizure-related injury is needed for long term atrophy. These regions frequently involve the mesial temporal lobe structures. To determine if the long term atrophy is related to an acute secondary injury, diffusion weighted MRI imaging will be done immediately after the occurrence of seizures is necessary to determine if an acute edematous insult has occurred or whether the long term atrophic changes are unrelated to edema. In this way, we are testing the hypothesis that the seizures lead to acute energy compromise in the hippocampus that will eventually result in atrophy. Given the difficulties in doing acute ictal PET scans, the MRI method appears more feasible for a targeted study. In addition, volumetric atrophy can be determined in those specific regions that are involved with acute intracellular edema.

Hypothesis 3: Traumatic brain injury does not result in acute hemorrhagic or non-hemorrhagic injury to the hippocampus.

Hypothesis 4: Acute post-traumatic seizures will result in acute intracerebral edema in hippocamapal structures (not initially injured by trauma) as measured by reductions in the apparent diffusion coefficient of the hippocampus.

Methods: The cEEG methods outlined in specific aim 1 will be followed. Three acute MRI scans will be done in this aim. Baseline MRI: Within 12 hours of injury, a high resolution (3 mm cuts) multimodality MRI (volumetric MP-RAGE, ADC, DWI, GRE, FLAIR) will be obtained to determine distribution of brain injury and to determine if any primary injury has affected the hippocampus. Primary injury will be considered positive if any of the following criteria are present: 1) ADC reduction < 500 u^2/sec, 2) GRE hypointensity, 3) FLAIR positivity. Seizure-

targeted MRI: Repeat MRI will occur within 4 hours of a documented electrographic seizure using the new UCLA CNRC. Surveillance MRI: Repeat MRI at 7 days after TBI will be obtained to determine if acute intracellular edema is present In the hippocampus that may have occurred due to non-seizure related secondary insults such as elevated intracranial pressure or brain ischemia. Automated cEEG seizure detection and presence of a neurointensive care fellow in the ICU 24 hours/day will facilitate prompt electrograpic diagnosis and targeted imaging. The incidence of elevated ICP or brain ischemia due to hypoxia or hypotension will be determined by prospective hourly monitoring of ICP and jugular venous oximtery.

Data Analysis: The locations of all primary injury types (ADC, GRE, FLAIR) will be defined categorically as cortical, subcortical, extra-hippocampal temporal, hippocampal and brainstem. Probabilistic maps of lesion location and the incidence of early post-traumatic seizures will be determined. The occurrence of seizure-associated hippocampal lesions (reduction in ADC and/or FLAIR) will be determined using both the seizure-related MRI sequence. The primary outcome will be the reduction in ADC below 675 u^2/sec. This threshold is selected based on our preliminary data (mean hippocampal ADC 995± 108 (3SD below the mean representing value of 675 u^2/sec). The volume of hippocampus involvement on the ipsilateral and contralateral sides will be determined using post-hoc analysis (Image J) and correlated with the extent of atrophy in specific aim 3.

Anticipated problems: Intracellular hippocampal edema may be seen in patients with early hypoxic injury following TBI, thus we will need exclude these subjects from this study. However, in previous reports, the incidence of these events is < 2% of all monitored hours (Vespa, 2003; Vespa 2005). The time course of changes in ADC are not well established after injury, hence it is unclear what the timing of scanning in comparison to seizure activity or the cessation of seizure activity should be. We will balance the demands for standard of care and patient safety with obtaining the imaging at the earliest possible time after seizures. Repeated measures and reliability of these measures for ADC has been previously demonstrated by our group at UCLA, mostly by repeated imaging of acute stroke patients (Kidwell, 2000). EEG electrode changes to accommodate MRI may be associated with lead placement variability, but marking these locations with semi-permanent markrs will reduce this error. The new neurointensive care unit with MRI suite adjacent to the ICU will make rapid imaging feasible.

Specific Aim 3: To determine if delayed hippocampal atrophy and conformational changes are greater in patients exhibiting post-traumatic seizures compared with those without early seizures.

Rationale: Experimental data from our laboratory has revealed that induced seizures early after fluid percussion injury results in selective loss of hippocampal CA3 cells (See preliminary data; Roncati-Zanier 2003). This cell loss is thought to be due to increased vulnerability of the hippocampal cells to the early secondary excitotoxicity and corresponds with a secondary glutamate surge as seen on cerebral microdialysis monitoring in the rat. Similar changes in cerebral microdialysis have been seen in humans with spontaneous early post-traumatic seizures and extensive hippocampal atrophy has been demonstrated ipsilateral to the seizure focus in several example patients. This degree of atrophy is in excess of those patients without early seizures. Hippocampal atrophy is associated with serious cognitive deficits after injury and protection of the hippocampus from secondary injury from early seizures is a novel therapeutic goal of cEEG monitoring.

Hypothesis 5: Delayed hippocampal atrophy is greater in patients exhibiting post-traumatic seizures compared with those without early seizures.

Hypothesis 6: Delayed changes in hippocampal conformational changes in CA2 region is greater in patients exhibiting post-traumatic seizures compared with those without early seizures.

Subjects: 100 TBI patients with GCS 3-13 over 5 years of study.

Methods: The methods in aim 1 will be followed for cEEG. Within 24 hours of injury, a high resolution volumetric MRI (MP-RAGE) will be obtained and will be repeated at 6 months after injury. Subjects with primary traumatic injury to the mesial temporal lobe will be excluded from analysis. Imaging analysis will be facilitated by the UCLA LONI (see detailed methods) with semi-automated registration, skull stripping, and volumetric analysis. Volumetric analysis of the whole brain and each hippocampus will be obtained for each subject. The percentage change in volumes between the initial 24 hour MRI and the 6 month MRI will be calculated for each subject. The ratio of percent change of each hippocampus to the entire brain will be calculated for each subject. The hippocampus ipsilateral to the seizure, or seizure onset for generalized seizures, will be identified. The percent atrophy of the ipsilateral and contralateral hippocampus will be ascertained and averaged across all subjects with early post-traumatic seizures.

To determine the conformational change in the hippocampus, application of an innovative algorithm sensitive to surface changes of the hippocampus (Frisoni et al, 2006; Apostolova 2006). This algorithm permits the generation of a 3D parametric mesh model of each hippocampus. The tracings include the hippocampus proper, dentate gyrus, and subiculum. Radial atrophy maps will then be drawn to determine regional conformational changes in CA1, CA2, CA3 and subiculum, that occur after TBI. Given our preliminary animal data (Roncati-

Zanier, 2003), we hypothesize that patients with early post-traumatic seizures will have regional CA3 atrophy.

Data Analysis: The expected rate of background post-traumatic hippocampal atrophy in the non-seizure group is 10.1% ± 0.6%. In our preliminary data from post-traumatic seizure patients, the extent of atrophy was 32% ± 2.4%. A power analysis was performed to determine the sample size of 60 patients total to determine a difference at the $p< 0.05$ level (80% power). Thus assuming an attrition rate of 30% due to death or inability to complete all aspects of follow-up (in Specific Aims 3 and 4), we propose to enroll 100 patients. We prospectively will evaluate unilateral and bilateral hippocampal atrophy in seizure patients, and compare the extent of atrophy ipsilateral and contralateral to the seizure focus to that of the global atrophy of non-seizure patients. In addition, regional changes in hippocampal subregions will be compared between non-seizure and seizure patients and to a group of age-matched controls (already being collected in ongoing TBI study at UCLA). A preliminary binary analysis of group differences in atrophy in any subregion compared with non-seizure patients, with our primary endpoint being a 10 difference in CA3 regions (based on our preliminary animal data, Roncati-Zanier 2003).

Potential Problems and Alternative Methods: Primary hemorrhagic injury of the mesial termporal lobe structures could result in enhanced atrophy without the occurrence of seizures and confound the control group. Exclusion of such cases will require an increment in the sample size, which we have accounted for. Additional non-epileptic secondary insults, such as anoxia and increased intracranial pressure, may lead to hippocampal injury and atrophy. We will exclude from the control group those non-epileptic patients who demonstrate acute FLAIR or DWI hyperintensities in the hippocampi from long term volumetric analysis. The diverse injury severity of the study group, with GCS 3-13 being studied, creates the possibility of variance in the extent of tissue atrophy, but the use of the ratio of hippocampal to whole brain atrophy, should control for this variability.

Specific Aim 4: To determine if the occurrence of post-traumatic seizures results in worsened memory-related cognitive outcome compared with patients without post-traumatic seizures.

Rationale: Post-traumatic seizures result in transient secondary increases in glycolytic activity and excitotoxicity. These secondary neurochemical events potentially could lead to additional cellular injury. Our preliminary data suggest that the cumulative burden of this secondary insults, as expressed by the cumulative burden of increased lactate/pyruvate ratio, corresponds to worsened cognitive outcome. The long term effects of non-traumatic status epilepticus prominently feature amnestic syndromes and other cognitive deficits (Adachi,

2005). Since the primary long term-deficit after TBI is neurocognitive compromise, and the degree of temporal lobe atrophy corresponds with impaired outcome (Wilde and Levin, 2005), it is reasonable to suspect that early post-traumatic seizures would result in a worsened state of cognitive function. This impairment may be related to a seizure-related induced secondary injury or from the side effects of anticonvulsant treatment. Stopping early post-traumatic seizures would be a unique therapeutic target that may enhance long-term cognitive outcome. The use of specific memory-related cognitive testing has specificity for mesial temporal lobe (hippocampal tissue) atrophy (Giavognoli, 2005; Bell, 2005).

Hypothesis 7: Early post-traumatic seizures will be associated with worsened memoery-neurocognitive outcome compared with age and severity matched TBI patients without early post-traumatic seizures.

Subjects: 100 TBI patients with GCS 3-13 over 5 years of study.

Methods: All subjects outlined in specific aim 1 will be closely followed for 1 year via telephone contact and office visits. At 3, 6 and 12 months, a detailed neuropsychological testing battery will be administered by an experienced psychometrician. The test battery will consist of measures of global outcome (Glasgow Outcome Score, extended), global cognitive function and regional assessments of temporal lobe function, specifically testing of verbal and non-verbal memory. The exact tests to be administered are contained in the detailed methods. Dr. Harvey Levin will supervise the psychometricians as outlined in the detailed methods and is one of the preeminent scientists in cognitive outcome after TBI.

Data Analysis: Within subject analysis of the 3, 6 and 12 month neuropsychological test results compared with early seizure incidence will be undertaken. Global neuropsychological outcome measures will be compared with the incidence of generalized seizures and the cumulative burden of spikes. In addition, regionally specific measures of mesial temporal function or short term memory (see outline of testing in detailed methods) will be compared with regional temporal seizure activity and the cumulative burden of temporal spikes. For data analysis, the laterality of seizure onset as well as the laterality of the primary brain injury contusion will be used as covariates to determine if laterality of injury plays an independent role in predicting memory-related cognitive tasks. Given the wide age range of our cohort, an age correction analysis will be undertaken to assess the impact of age on the relationships between seizure incidence and spike burden and temporal-lobe dependent cognitive tasks. In addition to direct comparison of test results, the rates of improvement in test results will be compared with the initial seizure incidence and spike burden.

Anticipated Problems and alternative methods: The heterogeneity of the primary injury as well as that of the presumed secondary injury (seizures) may make it

difficult to assess whether the differences in neuropsychologic outcome are due to the primary injury or the superimposed seizures. However, to date neurocognitive outcomes after TBI have not been demonstrated to be a result of specific anatomic sites of damage or the cumulative burden of damage. Rather, global measures such as GCS have been reliable indicators of expected outcome. Hence, we plan on standardizing the outcomes by controlling for GCS as well as the regions of primary contusional injury in considering whether early post-traumatic seizures worsen cognitive outcome. The sample size (100) should be sufficient to do this comparison. In addition, seizure patients may be exposed to anticonvulsant medications for longer periods of time during the recovery period, and the presence of these agents have well-established effects on outcome testing (Dikmen, 2000). Finally, differences between injury to dominant versus non-dominant hippocampi may affect the results of selected testing, but given our preliminary data demonstrating enhancement of bilateral hippocampal atrophy in seizure patients (preliminary data C8), we anticipate that these effects on selected testing will be identifiable.

Time Line: This study is expected to begin in January 2007 and continue with data accrual for 4 years. Aims 1-2 will continue through years 1-4, and aims 3-4 will continue from years 1-5. Data analysis will begin at year 3, and final data analysis be completed by year 5.

Yearly Time-Line:

Acute Studies cEEG/MRI tests	**Seizure MRI targeted study**	**MRI Volumetric Processing**	**Follow-up MRI/Cognitive**
Initial MRI 0-24 hours	30- 60 minutes after seizure onset	1-4 months	6 months
cEEG 0- 7 days			

4 Year Study Time Line:

Patient Recruitment, acute EEG, MRI, cognitive testing– years 1-4
MRI Volumetric Analysis – Years 2-4
Analysis of test results – Years 2-4
Preliminary reporting – Year 3
Final reporting – Year 4

The following institutions will be involved:
- University of California Los Angeles Medical Center
- Walter Reed Army Medical Center
- National Naval Medical Center

Investigators are:
- Paul Vespa, MD, (UCLA neurointensivist) (Principal Investigator)
- LCDR Etienne Mill (Neurologist at NNMC Bethesda)
- Col. Rocco Armonda, MD (Lead Neurosurgeon for TBI at USNMC Bethesda)
- CDR. Lisa Mulligan, MD (Integrated Service Chief of Neurosurgery NNMC)

PROGRESS REPORT SUMMARY ITEMS:

1. Enrollment in the civilian cohort of patients with cEEG and MRI study components has proceeded well. Enrollment at UCLA since 2008: 64 Civilian TBI patients. Active recruitment continues at this time. Data analysis is ongoing. Several publications have been resulted from this work (see list below). Ongoing data analysis is ongoing. The incidence of seizures in civilian TBI is 22%.
2. Development of imaging data warehousing, data transfer, and analysis of MRI data from UCLA and other potential study sites. We have collaborated closely with the UCLA Laboratory of Neurologic Imaging (LONI) and published several papers using the civilian TBI data that we have obtained (articles 1, 2, 5, 6, and 7).
3. Creation of the informatics infrastructure to perform remote continuous EEG monitoring and MRI at DOD sites. This involves maintaining a computer colocation facility and data flow into the facility. DISA B2B gate approval at DOD. Informatics infrastructure kept functional for the past 4 years in order to facilitate study at a DOD site. The informatics team has been writing new software that enables analysis of EEG using advanced processing techniques, and enabling other expert consultants, such as Dr. Jed Hartings (Univ Cincinnati) to process the EEG to search for other epileptic events that may not be visible to naked eye. We have published articles using this informatics structure (articles 2, 3, and 4).
4. Identification of a PI at Walter Reed National Military Medical Center (WRNMMC), initially Dr. Rocco Armonda, who after 1 year turned the study over to a neurologist, Dr. Mil Etienne. Dr. Etienne retired from the military. There is now an absence of personnel to continue the project at WRNMMC. Site visits to WRNMMC were performed. Repeat calls for a new site PI were requested of Dr. Armonda, but no progress to date. Dr. Armonda is also retiring from the military. A new potential PI is being sought but not yet identified.
5. Submission of IRB materials and negotiation with the IRB at WRNMMC. The local WRNMMC IRB took over 2 years to consider this proposal and

requested numerous changes, and has not issued final approval. IRB submission suspended at this time since there is no PI to represent the study.

6. Since we are not able to conduct this research at NNMC, as of November 2012 we are seeking new military sites such as Landstuhl Army Medical Center, the WRNMMC and SAMMC. We have identified potentially interested military doctors at these sites.

NARRATIVE OF PROGRESS AND PROBLEMS

The ongoing work for this project has consisted of weekly teleconferences for planning to get the EEG system at Bethesda NNMC upgraded to be on par with UCLA for the purposes of performing this project. These conferences include key personnel from NNMC, mostly Dr. Etienne Mil and the IT staff at NNMC. Several important roadblocks have been identified:

1) IRB approval at Bethesda (National Naval Medical Center): We have been unable enroll subjects for any component of this research at NNMC due to lack of IRB approval. Dr. Mill Etienne worked on the IRB submission, but the IRB submission has been delayed by the delays in IT approval.
2) Retirement of Dr. Etienne in 2012. Hence we lost a local PI. The IRB process at National Naval Medical Center stopped.
3) Trying to identify a new local PI at Landstuhl and WRNNMC (planned to search in 2013)

KEY RESEARCH ACCOMPLISHMENTS

1. Confirming the primary hypothesis in civilian TBI patients
2. Establishing an electronic gateway to the military medical centers for real time data capture.
3. Establishing working relationships with military neurosurgery and neurology departments.
4. Education of military doctors about the influence of seizures in TBI patients.
5. Several publications in leading journals.
6. Establishing continuous EEG monitoring as standard of care for severe TBI patients within the military.

REPORTABLE OUTCOMES IN THE FORM OF PUBLICATIONS

1. Alger JR, Schaewe TJ, Lai TC, Frew AJ, **Vespa PM**, Etchepare M, Liebeskind DS, Saver JL, Kidwell SC. Contrast agent dose effects in

cerebral dynamic susceptibility contrast magnetic resonance perfusion imaging. J Magn Reson Imaging. 2009 Jan;29(1):52-64.

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CONCLUSION:

We have conducted our research in civilian TBI with very promising results that suggest an association between early post-traumatic seizures and delayed hippocampal atrophy. The results from the civilian work has led to implementation of cEEG as a standard of care in military medicine. We continue to work on establishing the proper infrastructure at NNMC to start studying military TBI.

REFERENCES: none

APPENDICES:

1. Journal article in press: "Nonconvulsive Seizures after Traumatic Brain Injury are Associated with Hippocampal Atrophy". **Neurology. 2010 Aug 31;75(9):792-8. PMID: 20805525.**